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Editorials

Sodium Regulation During Ischemia Versus Reperfusion and Its Role in Injury

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There are considerable data to support the general hypothesis that accumulation of $[\text{Na}^+]_i$ during ischemia and early reperfusion leads, via $\text{Na}^+/\text{Ca}^{2+}$ exchange, to elevated $[\text{Ca}^{2+}]_i$, resulting in myocardial damage.^{1 2 3 4 5 6 7 8 9 10} Despite the strong support for the general aspects of this hypothesis, there is controversy regarding some details that have important implications for the design of therapeutic interventions. The relative importance of the increase in $[\text{Na}^+]_i$ during ischemia versus the increase in $[\text{Na}^+]_i$ during reperfusion in contributing to the rise in $[\text{Ca}^{2+}]_i$ and resultant injury is debated. These issues are important because it has been suggested that inhibition of the Na^+/H^+ exchanger (NHE) during reperfusion alone would be beneficial. This would allow clinical intervention after an ischemic episode. It is also important to understand why an increase in $[\text{Na}^+]_i$ is detrimental. It is commonly assumed that $[\text{Na}^+]_i$ is detrimental because it leads to increased $[\text{Ca}^{2+}]_i$ during reperfusion, either due to diminished Ca^{2+} efflux via $\text{Na}^+/\text{Ca}^{2+}$ exchange or due to increased Ca^{2+} influx due to reverse $\text{Na}^+/\text{Ca}^{2+}$ exchange. Recent data presented by Cross et al⁹ suggest that reverse $\text{Na}^+/\text{Ca}^{2+}$ exchange is involved in postischemic contractile dysfunction. However, an increase in $[\text{Na}^+]_i$ could also be detrimental because of effects on K^+ loss¹¹ or energetics. An understanding of the mechanism responsible for the detrimental effects of Na^+ accumulation is important for the design of therapeutic interventions. A study¹² published in this issue of *Circulation Research* adds new insight into these important issues.

What Is the Relative Contribution of Na^+ Entry During Ischemia Versus Reflow?

Lazdunski et al¹ originally hypothesized that during ischemia, protons will accumulate in the cell and in the extracellular space, and the low pH_o would inhibit NHE. On reperfusion, restoration of normal pH_o would stimulate NHE, leading to a rapid increase in $[\text{Na}^+]_i$, which would in turn stimulate $\text{Na}^+/\text{Ca}^{2+}$ exchange, leading to $[\text{Ca}^{2+}]_i$ overload. If this hypothesis is correct, addition of NHE inhibitors at the start of reflow should reduce $[\text{Ca}^{2+}]_i$ overload and be protective. However, there are conflicting data regarding the protective effects of NHE inhibitors. NHE inhibitors are protective if administered before or during ischemia; however when NHE inhibitors are administered at the start of reperfusion, there are data suggesting protection, partial protection, and no protection (see Murphy et al¹⁰ and references within). In perfused heart models, measurements of pH_i , $[\text{Na}^+]_i$, and $[\text{Ca}^{2+}]_i$ during ischemia and reflow have shown a rise in $[\text{Na}^+]_i$ and $[\text{Ca}^{2+}]_i$ during ischemia.^{3 5 6 8} The original model of Lazdunski et al¹ assumed that NHE would not contribute much to the rise in $[\text{Na}^+]_i$ during ischemia because of the low pH_o .¹ Although low pH_o reduces activity of NHE, Vaughan-Jones et al¹³ have shown that NHE can still operate. It is also suggested that other mechanisms such as the noninactivating Na^+ channels contribute to the rise in $[\text{Na}^+]_i$ during ischemia.¹⁴ The mechanism responsible for the rise in $[\text{Na}^+]_i$ is debated,^{10 14} but it is likely that both Na^+/H^+ exchange and noninactivating Na^+ channels contribute. Imahashi et al¹² show that the amount of $[\text{Na}^+]_i$ that exchanges with $[\text{Ca}^{2+}]_o$ is dependent on the amount of $[\text{Na}^+]_i$ accumulated during ischemia, as well as the relative rates at which $[\text{Na}^+]_i$ is extruded via $\text{Na}^+/\text{Ca}^{2+}$ exchange relative to other Na^+ extrusion mechanisms. In agreement with other investigators, Imahashi et al¹² clearly demonstrate that accumulation of $[\text{Na}^+]_i$ during ischemia is an important source of the $[\text{Na}^+]_i$ that exchanges with Ca^{2+} on reperfusion.

Lazdunski et al¹ hypothesized that activation of Na^+/H^+ exchange on reflow would lead to an increase in $[\text{Na}^+]_i$, which would lead to reversed $\text{Na}^+/\text{Ca}^{2+}$ exchange. Interestingly, most investigators^{6 8 10} including Imahashi et al¹² report a decline in $[\text{Na}^+]_i$ on reperfusion. Imahashi et al acknowledged in their discussion that although NHE "produced massive Na^+ influx to remove H^+ during ischemic acidosis, this inhibition did not significantly alter $[\text{Na}^+]_i$ kinetics during reperfusion" (page 1405). They speculate that Na^+ influx via NHE during reperfusion is markedly smaller than Na^+ efflux pathways. An important finding of Imahashi et al is that Na^+ efflux via $\text{Na}^+/\text{Ca}^{2+}$ exchange is a major Na^+ efflux pathway during reperfusion. Van Emous et al¹⁵ have shown the importance of the Na^+-K^+ ATPase to Na^+ efflux during reperfusion. They reported that inhibition of the Na^+-K^+ ATPase unmasks the increase in $[\text{Na}^+]_i$ that occurs on reperfusion by showing that in the presence of ouabain there is an increase in Na^+ on reperfusion. They also showed that the increase in Na^+ is lower in the presence of EIPA, implying that NHE is active during early reperfusion. Imahashi et al¹² also conclude that their data, which show that inhibition of Na^+/H^+ exchange during reperfusion does not alter Na^+ efflux kinetics, are "inconsistent with the hypothesis that Na^+ entry via Na^+/H^+ exchange just after reperfusion is a critical trigger for reperfusion injury" (page 1405). This point may require additional study. Although the data are

convincing that Na^+ entry during ischemia is a major regulator of ionic changes during early reperfusion, it is difficult to exclude a role for Na^+ entry during the first few seconds of reperfusion. It is likely that, depending on the experimental model, Na^+ entry via Na^+/H^+ exchange on reperfusion will contribute to Ca^{2+} entry and $[\text{Ca}^{2+}]_i$ overload. Studies by Tani and Neely,³ who measured calcium uptake using $^{45}\text{Ca}^{2+}$, have shown that inhibitors of Na^+/H^+ exchange given only at reperfusion attenuate $^{45}\text{Ca}^{2+}$ uptake on reflow; the reduction in $^{45}\text{Ca}^{2+}$ uptake was greater when amiloride was added during ischemia and reperfusion, but there was a slight (but not significant) attenuation of $^{45}\text{Ca}^{2+}$ uptake when amiloride was added only at reflow. It is likely that some of the Na^+ that enters via Na^+/H^+ exchange at the start of reperfusion will exchange with Ca^{2+} and contribute to $[\text{Ca}^{2+}]_i$ overload. Furthermore, the first few seconds of reperfusion are most important for Na^+ entry via NHE, and it is possible that when EIPA is added at the start of reperfusion, it does not reach the myocytes soon enough to be effective. This might account for the lack of effect of EIPA on the rate of Na^+ efflux.

Taken together, the data in the literature and the data of Imahashi et al¹² suggest that the accumulation of $[\text{Na}^+]_i$ during ischemia accounts for a large proportion of the $[\text{Na}^+]_i$ that exchanges with Ca^{2+} on reperfusion. However, Na^+ entry via NHE during the first seconds of reperfusion may also be important. Regardless of the proportion of $[\text{Na}^+]_i$ that enters during ischemia versus reperfusion, an elegant series of studies^{2, 7} have shown that manipulations that attenuate $\text{Na}^+/\text{Ca}^{2+}$ exchange at the start of reperfusion such as lowering perfusate Ca^{2+} , raising $[\text{Na}^+]_o$, or acid reperfusion all reduce postischemic contractile dysfunction. Data presented by Imahashi et al¹² enhance these earlier studies by showing that low Ca^{2+} reperfusion reduces the rate of Na^+ efflux, consistent with inhibition of $\text{Na}^+/\text{Ca}^{2+}$ exchange, providing support for the conclusion that inhibition of $\text{Na}^+/\text{Ca}^{2+}$ exchange during reperfusion is beneficial.

Why Is an Increase in $[\text{Na}^+]_i$ Detrimental?

Imahashi et al¹² demonstrate that it is the elevated $[\text{Na}^+]_i$ at the start of reperfusion, which exchanges with Ca^{2+} , that is responsible for postischemic contractile dysfunction. They show that hearts that have nearly identical $[\text{Na}^+]_i$ levels at the end of ischemia have differences in postischemic contractile dysfunction, which correlate with differences in the rate of $\text{Na}^+/\text{Ca}^{2+}$ exchange during reperfusion. The data show that slowing Na^+ extrusion, by reducing $[\text{Ca}^{2+}]_o$, improves postischemic function, and that enhancing Na^+ extrusion by elevating $[\text{Ca}^{2+}]_o$ worsens postischemic contractile function. In addition, perfusion with a $\text{Na}^+/\text{Ca}^{2+}$ exchange inhibitor reduces the rate of Na^+ extrusion and improves postischemic contractile function. The data presented by Imahashi et al¹² clearly show that it is not the amount of $[\text{Na}^+]_i$ accumulated during ischemia or reperfusion that results in postischemic contractile dysfunction; rather, it is the amount of $[\text{Na}^+]_i$ that exchanges with Ca^{2+} that influences recovery of function. These data combined with data in the literature suggest that inhibition of $\text{Na}^+/\text{Ca}^{2+}$ exchange on reperfusion may be a promising therapeutic target.

Footnotes

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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